

**This Page Is Inserted by IFW Operations  
and is not a part of the Official Record**

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

13 were rejected under 35 USC §102(a) as being anticipated by Powell et al.; and Claims 1-13 were rejected under 35 USC §103(a) as being unpatentable over Weissman et al. and Hansson et al.

Applicants have canceled dependent Claims 8 and 12.

Applicants have amended Claim 7 to correct informalities, i.e. to correct the misspelled term "metoprolol."

Applicants have added new Claims 14-17. Applicants' pending application now contains 4 independent claims and a total of 15 claims. An additional fee of \$42.00 is enclosed for the extra independent claim.

**35 USC §112, second paragraph rejections:**

The Office rejected Claim 9 under 35 USC §112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. Applicants have amended Claim 9 to include the step of administering the single dosage unit to a patient. <sup>1</sup>

In light of Applicants' amendment presented, Applicants respectfully submit that the 35 USC §112, second paragraph rejection of Claim 9 has been successfully traversed. Allowance is therefore requested.

**35 USC §102(b) rejections:**

The Office has rejected Claims 1-7, 9-11 and 13 under 35 USC §102(a) as anticipated by Powell et al. Applicants respectfully traverse.

Applicants have amended Claims 1 and 9. Claim 1 includes the use of “consisting essentially of” language to close the claim to include only beta-blockers and platelet inhibitors but to leave it open only to the inclusion of ingredients that do not materially affect the basic and novel characteristics of Applicants’ invention. Claim 9 also includes the use of “consisting essentially of” language to close the step of formulating the single dosage to include only beta-blockers and platelet inhibitors but to leave it open only to the inclusion of ingredients that do not materially affect the basic and novel characteristics of Applicants’ invention. On the other hand, Powell’s device requires the use of a vasopeptidase inhibitor singly or with other ingredients. Applicants now claim a single dosage unit that is closed to ingredients that materially affect the basic characteristics of Applicants’ invention. A vasopeptidase inhibitor to treat and/or relieve the symptoms of angina pectoris would materially affect the basic characteristics of Applicants’ invention. Thus, Powell can no longer anticipate Applicants’ Claims 1 or 9.

In light of Applicants’ amendments and the arguments presented, Applicants respectfully submit that the 35 USC §102(a) rejection of Claims 1-7, 9-11 and 13 has been successfully traversed. Allowance is therefore requested.

**35 USC §103(a) rejections:**

The Office has rejected Claims 1-13 under 35 USC §103(a) as being unpatentable over Weissman et al. and Hannsson et al. (AB). Applicants respectfully traverse.

Applicants have canceled Claims 8 and 12. The rejection as it pertains to these claims is now moot.

Applicants have amended Claims 1 and 9 and have added new independent Claims 14 and 16. Claims 1 and 9 have been amended as previously described.

Claims 1, 9 and 14 are now limited to a formulation that consists essentially of a beta-blocker and a platelet inhibitor. Claim 16 is now limited to a formulation that consists essentially of a beta-blocker and aspirin.

Applicants believe a brief overview of the problems Applicants' invention is attempting to solve and the proposed solution will help the Office better understand the patentability of the present invention. The present invention is based upon recognizing the serious consequences stemming from a failure of patients to avail themselves of, to receive and to take medication (in other words, patient compliance), particularly beta-blockers and platelet inhibitors. The present application teaches that despite compelling clinical evidence, many individuals at risk fail to benefit from such treatment. (Applicants' Disclosure: Page 2, lines 8-9). Large studies indicate that tens of thousands of lives could be saved each year if more people were utilizing a beta-blocker after having a heart attack. (Applicants' Disclosure: Page 2, line 26 to Page 3, line 2). The failure of patients to avail themselves of such treatment underscores the present need for the formulations of the present invention. (Applicants' Disclosure: Page 4, lines 16-18).

Furthermore, the importance of platelet inhibitors (particularly aspirin) may be trivialized by lay individuals because of their familiarity. Some individuals instructed to

take both a prescription medication and aspirin presume that the prescription is more potent. Consequently, they fail to adhere to taking aspirin. Exhibit 1 (JR Knight, J Clin Pharm Ther, 1991) attached hereto is evidence of the compliance problem, particularly when one medication is prescribed and the other is an over-the-counter product that is perceived as a symptomatic drug. Exhibit 1 describes an abstract of a study of knowledgeable non-compliance with prescribed drugs in elderly subjects, a study with particular reference to non-steroidal anti-inflammatory and antidepressant drugs. The study involved taking one of the above drugs, and at least one other prophylactic or symptomatic drug. Non-steroidal anti-inflammatory drugs and antidepressant drugs are commonly regarded as symptomatic only and knowledgeable non-compliance is consequently high. They are also regarded as less important than drugs which produce no immediate relief of symptoms but which the patient recognizes as needing to be taken regularly to maintain health.

Applicants recognized the problems of achieving compliance, which includes the inconvenience of taking multiple dosage units over a long period of time, the lack of immediately noticeable beneficial effects, trivialization of common medications such as aspirin, and inconvenience of the requirement to obtain some medications by prescription and some over-the-counter. (Applicants' Disclosure: Page 3, lines 16-24). Applicants recognized that many of the above mentioned problems can be ameliorated by incorporating the desired beta-adrenergic blocking agents and antagonists of platelet function into a single dosage unit. (Applicants' Disclosure: Page 3, lines 25-26).

Applicants particularly note that the problems of trivialization and non-compliance

with aspirin and the requirement to purchase it over-the-counter are ameliorated by combining aspirin with a prescription medication such as beta-adrenergic blockers. Beta-adrenergic blockers are listed in the Physician Desk Reference and are dispensed by prescription.

The Office states that Hannsson et al. teach the combination of aspirin and a beta-blocker to be useful for treatment of hypertension. Applicants respectfully traverse.

Hannsson teaches individually titrating beta-receptor antagonists and administering them and aspirin separately. (See Methods in Hannsson et al.). Hannsson et al. were not concerned with patient compliance issues. The principal aims of the Hannsson et al. study were: to assess the association between major cardiovascular events (non-fatal myocardial infarction, non-fatal strokes, and cardiovascular death) and the target blood pressures <90 mm Hg, <85 mm Hg, and <80 mm Hg during antihypertensive treatment; to assess the association between major cardiovascular events and the diastolic blood pressure achieved during treatment; and to find out whether the addition of low doses of acetylsalicylic acid to antihypertensive treatment reduces the rate of major cardiovascular events. (See Hannsson et al.; Page 2, column 1, second paragraph). Nowhere in Hannsson et al. does it suggest the use of a single dosage unit consisting essentially of a beta-blocker and aspirin. In fact, the treatment protocol was to treat with separate drugs in four further steps. (See Hannsson et al.; Page 2, column 2, first paragraph under '*Treatment*').

The Office admits that Hannsson et al. does not teach the addition of B vitamins

such as folic acid, B12 and B6.

The Office states that Weissman et al. teach acetylsalicylic acid (aspirin) combined with at least one of cyanocobalmin (vitamin B12), a folic acid compound, and a pyrodoxine compound (Vitamin B6), but does not teach the addition of a beta-blocker.

The Office relies on its rejection by stating that it is prima facie obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. Applicants respectfully direct the Office's attention to Applicants' disclosure. Applicants disclose that beta-blockers and platelet inhibitors exist in the prior art. Applicants do not presume to claim that these medications are new. Applicants' invention contemplates an interventional measure that is neither within the scope of lay individuals nor presently available to lay individuals. As discussed in Applicants' disclosure, there is a need for cardiovascular preventive treatment and a need to overcome a failure of patients to avail themselves of such treatment. This underscores the need for the formulations of the present invention. Combining these agents to provide a single dosage unit for a user would simplify treatment, increase convenience, reduce cost, and enhance compliance with the use of medications that require long-term use.

The Office presumes that "one of ordinary skill in the art would have been motivated to incorporate all agents herein together in a single dosage unit because they are known to be useful for the same purpose.

Applicants' invention was conceived to provide the claimed cardiovascular

medicaments in a single dosage unit for a user to help alleviate existing and on-going, long-term problems. Specifically, Applicants' invention is an attempt to simplify treatment, increase convenience, reduce cost, and enhance patient compliance, particularly in older patients where cardiovascular treatment regimens require taking multiple medications over long-term treatment periods.

Not only does Applicants' invention represent an attempt to provide a prophylactic therapy in a single dosage unit to address the above-mentioned problems, but Applicants' invention also attempts to improve upon the under-utilization of these specific medications, namely beta-blockers and platelet inhibitors. Under-utilization is clearly a concern of the medical profession. Particularly, health plan organizations are continually looking for effective ways to improve health outcomes and lower costs.

Applicants provide herewith Exhibit 2, which is a study/investigation by McCormick et al. entitled "Use of aspirin, beta-blockers and lipid lowering medications before recurrent acute myocardial infarction: Missed opportunities for prevention?", Arch Intern Med, Vol 15, March 22, 1999, pages 561-567. This study addresses the concern that aspirin, beta-blockers and lipid lowering medications are under utilized.

Exhibit 3 is a report from Hedis 2000, a publication that reports upon the quality of health care in the United States. It states that only 10% of MCOs (managed care organizations) had an acceptable rate of beta-blocker treatment after a heart attack. The report concluded that if the remaining organizations that were studied performed similarly, more than 2000 cardiac deaths and tens of millions of dollars would be reduced annually.



Exhibit 4 is an abstract from the Journal of the American Geriatric Society (1999) on the underutilization of aspirin in older patients with prior myocardial infarction at the time of admission to a nursing home. The conclusion is that there is a marked underutilization of aspirin in the treatment of older patients with documented prior myocardial infarction at the time of admission.

Exhibit 5 is an abstract from the Canadian Journal of Cardiology (1999) on the under use of acetylsalicylic acid (aspirin) in individuals with myocardial infarction, ischemic heart disease or stroke. It concludes that acetylsalicylic acid appears to be underused in those at high risk for future vascular events.

Further, the solutions to problems with compliance and under-utilization of helpful medications for cardiovascular treatments are elusive, and have troubled the healthcare industry for a long time. The industry continues to struggle to find answers to these perplexing questions. The healthcare industry's focus is now and has always been to educate physicians and patients, not to providing novel means for achieving better patient compliance and utilization results.

The present application specifically addresses the failure of patients to receive these treatments and seeks to improve upon it, as stated on Page 4, lines 16-18 of Applicants' disclosure:

The clear need for cardiovascular preventive treatment and the failure of patients to avail themselves of such treatment underscores the present need for the formulations of this invention.

Nowhere in any of the cited prior art is it suggested to combine these particular multiple medicaments (beta-blockers and platelet inhibitors, e.g. aspirin) into a single

dosage unit to simplify treatment, increase convenience, reduce cost and enhance patient compliance. The haphazard combining of medications, even those known to have cardiovascular usage, would not improve upon this problem.

Similarly, this problem has been overlooked by the pharmaceutical industry despite considerable motivation, i.e. increased sales, to increase usage of medication.

Applicants submit that without some teaching or suggestion in the prior art that addresses solutions to the problem of the failure of patients to receive specific cardiovascular treatments, the present invention would be obvious only in hindsight.

It is clear from Applicants' disclosure that Applicants' invention is a combination of old elements. In determining obviousness, "the inquiry is not whether each element existed in the prior art, but whether the prior art made obvious the invention as a whole for which patentability is claimed." Hartness International, Inc. v. Simplimatic Engineering Co., 819 F.2d 1100, 2 USPQ2d 1826 (Fed. Cir. 1987). If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit one to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.' In re Rouffet, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998). When the patented invention is made by combining known components to achieve the new system, the prior art must provide a suggestion or motivation to make such a combination. Heidelberger Druckmaschinen AG v. Hantscho

Commercial Prods., Inc., 21 F.3d 1068 (Fed. Cir. 1994). It is insufficient that the prior art shows similar components, unless it also contains some teaching, suggestion, or incentive for arriving at the claimed structure. Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931 (Fed. Cir. 1990). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention. Smiths Industries Medical Systems, Inc. v. Vital Signs, Inc., 50 USPQ2d 1641, *superseded on rehearing*, 183 F.3d 1347, 51 USPQ2d 1415 (Fed. Cir. 1999).

It is clear that when Applicants' invention is viewed as a whole the prior art contains no suggestion to combine Applicants' cardiovascular treatment medications into a single dosage unit. Where Applicants' components are similar to those components shown and disclosed in the prior art, the law requires that the prior art also contain some teaching, suggestion or incentive for arriving at Applicants' claimed structure. The Office has failed to provide this showing. The Office states that one of ordinary skill in the art would have been motivated to combine the medications into a single dosage unit because they are known to be useful for the same purpose. The Office relies on its conclusion based on In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

The Office's reliance is misplaced and Kerkhoven is inapposite. Kerkhoven is a process claim case and cites to In re Crockett, 279 F.2d 274 (CCPA 1960), which contains the reference that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a

third composition which is to be used for the **very sam purpose**. The ruling is based on the use of two compositions each of which promotes the formation of a nodular structure in cast iron. The ruling in Kerkhoven is inappropriate in the present application because the two compositions of the present application are not used for the **very same purpose**. The purpose of beta-blockers is to block nerve impulses to special sites (beta receptors) and to reduce the rate of heartbeats and the force of heart contractions. The purpose of platelet inhibitors is to inhibit the action of the blood clotting element (platelets) in the blood. In other words, beta-blockers cannot be used for inhibiting platelet action in the blood. Where the purpose of beta-blockers and platelet inhibitors are **not the same**, Kerkhoven is inapposite.

In accordance with the more recent rulings of the Federal Circuit, the Office must point to some teaching, suggestion or incentive in the cited prior art for arriving at the claimed structure. The Office has failed to do this. On the other hand, Applicants have provided evidence of the under-utilization of medications and the Declaration of Dr. Dean as to the healthcare industries' struggles to find answers to these perplexing questions.

In light of the above amendments and arguments, Applicants respectfully submit that Claims 1-7, 9-11 and 13-17 of the present application contain allowable subject matter and that the previous 35 USC §§ 112, second paragraph, 102(a) and 103(a) rejections have been successfully traversed.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,



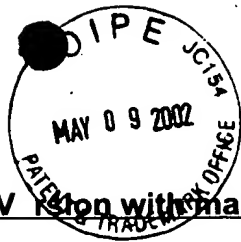
Dated: 4/30/02

Robert R. Deleault, Reg. No. 39,165  
Attorney for Applicants  
41 Brook Street  
Manchester, NH 03104  
Tel. (603) 668-1971

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on:

April 30, 2002  
Robert R. Deleault  
Robert R. Deleault



COPY OF PAPERS  
ORIGINALLY FILED

---

V ~~Not~~ with markings to show changes made

1. (Amended) A medicament dosage unit [comprising] consisting essentially of a beta-adrenergic blocker and a platelet inhibitor.
  
7. (Amended) The dosage unit of Claim 1 wherein said beta-adrenergic blocker is [metoprolol] metoprolol.
  
9. (Amended) A method of treating cardiovascular disease said method comprising: formulating a single dosage unit [comprising] consisting essentially of a beta-adrenergic blocking agent and a platelet inhibitor[.]; and administering said single dosage unit to a patient.

# Exhibit 1

J Clin Pharm Ther 1991 Apr;16(2):131-7

Knight JR, Campbell AJ, Williams SM, Clark DW  
Department of Pharmacology, University of Otago Medical School,  
Dunedin, New Zealand.

Knowledgeable non-compliance with prescribed drugs in elderly subjects--a study with particular reference to non-steroidal anti-inflammatory and antidepressant drugs.

Knowledgeable non-compliance with non-steroidal anti-inflammatory drugs (NSAIDs) and antidepressant drugs was investigated in a community-based sample of elderly people. Everyone 70 years and over living in a defined area and taking one of the above drugs, and at least one other prophylactic or symptomatic drug, was studied. Non-steroidal anti-inflammatory drugs and antidepressant drugs are commonly regarded as symptomatic only and knowledgeable non-compliance is consequently high.

They are also regarded as less important than drugs which produce no immediate relief of symptoms but which the patient recognizes as needing to be taken regularly to maintain health. In our study, compliance with non-steroidal anti-inflammatory drugs and antidepressant drugs was highest in those who were compliant with a prophylactic drug and were also taking a symptomatic drug. The greater the number of tablets the patient was taking the more likely he or she was to be compliant with the NSAID. Compliance with NSAIDs and antidepressant drugs requires clear label instructions and the patient knowing the purpose of the medication.

PMID: 1856251, UI: 91310736

-----

## Exhibit 2

## ORIGINAL INVESTIGATION

# Use of Aspirin, $\beta$ -Blockers, and Lipid-Lowering Medications Before Recurrent Acute Myocardial Infarction

## Missed Opportunities for Prevention?

Danny McCormick, MD, MPH; Jerry H. Gurwitz, MD; Darleen Lessard, MS; Jorge Yarzebski, MD, MPH; Joel M. Gore, MD; Robert J. Goldberg, PhD

**Background:** For patients who have had a previous myocardial infarction (MI), the use of aspirin,  $\beta$ -blockers, and lipid-lowering agents reduces the risk of recurrent MI and death.

**Objectives:** To examine trends in and determinants of receipt of these 3 medications before hospitalization for recurrent acute MI (AMI).

**Methods:** The study population consisted of 1710 patients with a previous history of MI hospitalized with a validated recurrent AMI in all hospitals in Worcester, Mass, during 1986, 1988, 1990, 1991, 1993, and 1995. Logistic regression analyses were used to assess the effect of demographic, clinical, and temporal factors on the receipt of aspirin,  $\beta$ -blockers, and lipid-lowering medications before hospital admission for recurrent AMI.

**Results:** More than 47% of patients in each study year were not receiving each medication before admission, although significant increases in use were noted over time for aspirin (from 13.5% to 52.6%),  $\beta$ -blockers (from 33.2% to 44.4%), and lipid-lowering medications (from 0.8%

to 11.7%). In multivariate analyses, advancing age was associated with not receiving aspirin (odds ratio [OR], 0.67; 95% confidence interval [CI], 0.51-0.89), lipid-lowering medications (OR, 0.14; 95% CI, 0.08-0.25), and  $\beta$ -blockers (OR, 0.75; 95% CI, 0.57-1.00), although this effect was of borderline significance for  $\beta$ -blockers. Being a woman was associated with not receiving aspirin (OR, 0.78; 95% CI, 0.62-0.98) but was positively associated with receiving lipid-lowering medications (OR, 1.59; 95% CI, 1.04-2.43). Coexisting medical conditions and concurrent use of other cardiovascular medications were also associated with receipt of each medication.

**Conclusion:** Despite encouraging increases over time, the low absolute levels of receipt of medications shown to be efficacious in the long-term treatment of patients after an MI, and their variation by age and sex, suggest that substantial opportunities may exist to prevent recurrent AMIs through the increased use of aspirin,  $\beta$ -blockers, and lipid-lowering medications.

*Arch Intern Med.* 1999;159:561-567

From the Section for Health Services Research, Divisions of General Medicine/Primary Care/Geriatrics (Drs McCormick, Gurwitz, Yarzebski, and Goldberg) and Cardiovascular Medicine (Ms Lessard and Drs Yarzebski, Gore, and Goldberg), and the Meyers Primary Care Institute (Drs McCormick, Gurwitz, and Goldberg), University of Massachusetts Medical Center and the Fallon Healthcare System, Worcester.

**M**ORTALITY associated with a recurrent acute myocardial infarction (AMI) is appreciably higher than that associated with a first AMI. Several medications exist, however, that have been shown to reduce the likelihood of recurrent AMI and death in patients who have established coronary artery disease, including patients who have had an initial AMI. The effectiveness of therapy with aspirin,<sup>1-3</sup>  $\beta$ -blockers,<sup>3,9</sup> and lipid-lowering medications<sup>10-12</sup> in the secondary prevention of AMI has been well established in large, randomized clinical trials and/or meta-analyses of the published literature. It has been estimated that use of these medications can reduce the risk of cardiovascular death and nonfatal reinfarction, respectively, by 22% and 27% for  $\beta$ -blockers,<sup>3,9</sup> 13% and 31% for aspirin,<sup>1</sup> and

14% and 25% for all lipid-lowering medications combined.<sup>13</sup> Based on this evidence, widely publicized guidelines strongly recommend the routine long-term use of aspirin and  $\beta$ -blockers<sup>14,15</sup> in patients who recently had an AMI and lipid-lowering medications in patients with elevated cholesterol levels following hospital discharge after AMI.<sup>13,16</sup>

Despite the positive findings of studies examining the effectiveness of these therapies and the widespread dissemination of these practice guidelines, findings of several previous studies<sup>17-23</sup> suggest that these medications are underprescribed to patients at hospital discharge after an AMI. Results of previous studies also suggest that nonclinical factors such as age,<sup>17,21</sup> sex,<sup>20</sup> and type of medical insurance<sup>20</sup> may affect the likelihood of receiving these medications at hospital discharge after an AMI.



## PATIENTS AND METHODS

This investigation was conducted as part of the Worcester Heart Attack Study, a multihospital, population-based investigation of time trends in the attack and survival rates associated with AMI.<sup>24-26</sup>

### STUDY POPULATION

The population studied consisted of patients hospitalized with a primary or secondary diagnosis of AMI (*International Classification of Diseases*, Ninth Revision, code 410)<sup>27</sup> in all acute care general hospitals in the Worcester (Mass) Standard Metropolitan Statistical Area (1990 census estimate = 437 000) during 1986, 1988, 1990, 1991, 1993, and 1995, who had a history of myocardial infarction (MI). Sixteen university-affiliated and community hospitals were originally included in this study, with fewer hospitals included in recent study years because of hospital closures or conversions to long-term care facilities. The medical records of greater Worcester residents with a discharge diagnosis of AMI from these hospitals were individually reviewed and validated according to pre-established diagnostic criteria that have been described previously.<sup>30-32</sup> In brief, these criteria included a clinical history of prolonged chest pain not relieved by nitrate therapy or rest; increased total and isoenzyme subfractions of creatine kinase or lactate dehydrogenase; and serial electrocardiographic findings of ST segment changes or Q waves typical of AMI. At least 2 of these 3 criteria needed to be satisfied for study inclusion. Presence of a previous history of MI was assessed through information provided by the patient that was documented in the medical record at hospital admission and confirmed through review of the medical record of previous hospitalization for AMI at areawide hospitals.

### DATA COLLECTION

The hospital records of patients with validated AMI were abstracted for demographic (age, sex, and race) and clinical data (medical history of previous MI, angina, hypertension, diabetes, congestive heart failure, or stroke), type of medical insurance, total serum cholesterol level observed during hospitalization, and preadmission medication use (aspirin,  $\beta$ -blockers, lipid-lowering medications, calcium channel blockers, diuretics, warfarin sodium, antiarrhythmic medications, and digoxin). Patients were

considered to be taking a medication before admission if it was listed as a current outpatient medication in the medical record on the day of hospital admission for recurrent AMI. This information was provided by patients themselves, their usual outpatient physicians, or other referring institutions, such as long-term care facilities. Outpatient medical records were not used for verification of medical regimens.

### STATISTICAL ANALYSIS

Time trends in the use of aspirin,  $\beta$ -blockers, and lipid-lowering medications before hospitalization for recurrent AMI were analyzed by determining the percentages of patients who received each of these medications by study year. A 2-sided Cochran-Armitage test for trend was used to determine statistical significance.

Demographic and clinical correlates of receiving each medication were evaluated for the study sample (all study years combined), and relative risks and 95% confidence intervals (CIs) were calculated for each variable. These variables were used to develop separate stepwise multivariate logistic regression models with use of aspirin,  $\beta$ -blockers, and lipid-lowering medication as the outcome variables. Candidate variables in these analyses included race (white vs all other races), medical history (angina, hypertension, diabetes, congestive heart failure, and stroke), concurrent (preadmission) use of other medications (aspirin,  $\beta$ -blockers, lipid-lowering medications, calcium channel blockers, diuretics, warfarin, antiarrhythmic medications, and digoxin), medical insurance (private vs Medicare, Medicaid, and uninsured), and total serum cholesterol level observed in the hospital ( $\geq 5.17$  vs  $< 5.17$  mmol/L [ $\geq 200$  vs  $< 200$  mg/dL]). Complete lipid profile laboratory data were not available for study participants. Our definition of a high serum cholesterol level (total cholesterol level  $\geq 5.17$  mmol/L [ $\geq 200$  mg/dL]) was used to serve as a proxy for a low-density lipoprotein cholesterol level of approximately 3.36 mmol/L or greater ( $\geq 130$  mg/dL),<sup>10</sup> the level at which medical treatment of hypercholesterolemia in patients with established coronary heart disease is recommended by the National Cholesterol Education Project guidelines, published in 1994.<sup>13</sup> Variables were dropped from each model at a significance level of  $P < .05$ . Because of a priori importance, age ( $< 65$ , 65-74, and  $\geq 75$  years), sex, and study year (with 1995 as the referent category) were forced into all models. For each model, we reported adjusted odds ratios (ORs) and 95% CIs for all variables.

However, among patients experiencing recurrent AMI, little is currently known about the use of these medications before the event. Patients who have had a previous AMI are at particularly high risk for recurrent AMI and death; patients who have recurrent AMI and are not using these medications may thus represent missed opportunities for prevention. Understanding the factors associated with receipt of these medications for patients with recurrent AMI may help to overcome obstacles to optimizing their use.

The objectives of this observational, community-wide study were (1) to examine trends over time in the percentages of patients receiving aspirin,  $\beta$ -blockers, and lipid-lowering medications at hospital admission for re-

current AMI and (2) to identify factors that are associated with the receipt of these agents in patients with previous AMI.

## RESULTS

### PATIENT CHARACTERISTICS

The total study population comprised 1710 patients, most of whom were older than 65 years, male, and white, with no private medical insurance (**Table 1**). Coexisting medical conditions were common: 43.0% had angina, 58.1% had hypertension, 34.3% had diabetes, 31.2% had a history of congestive heart failure, and 36.2% had a total cho-

**Table 1. Bivariate Analysis of the Association of Various Characteristics With the Receipt of  $\beta$ -Blockers, Aspirin, and Lipid-Lowering Medications Before Hospital Admission for Recurrent Myocardial Infarction: Worcester Heart Attack Study, 1986-1995**

Characteristics	Patients, No. (%)	Risk Ratio (95% Confidence Interval)*		
		For Receiving Aspirin	For Receiving $\beta$ -Blockers	For Receiving Lipid-Lowering Medications
<b>Demographics</b>				
Age, y				
<65	475 (27.8)	(Referent)	(Referent)	(Referent)
65-74	476 (27.8)	0.93 (0.79-1.08)	0.97 (0.83-1.13)	0.71 (0.49-1.03)
$\geq 75$	759 (44.4)	0.81 (0.70-0.94)	0.81 (0.70-0.94)	0.23 (0.14-0.38)
Women	685 (40.0)	0.88 (0.76-0.98)	0.96 (0.85-1.08)	0.93 (0.55-1.31)
White	1593 (83.2)	1.09 (0.84-1.41)	0.76 (0.63-0.93)	1.43 (0.64-3.18)
Private insurance	552 (32.3)	1.02 (0.88-1.18)	1.02 (0.89-1.18)	1.57 (1.18-2.35)
<b>Medical history</b>				
Angina	735 (43.0)	1.24 (1.10-1.40)	1.41 (1.25-1.60)	1.11 (0.79-1.56)
Hypertension	993 (58.1)	1.12 (0.99-1.27)	1.56 (1.36-1.78)	1.17 (0.82-1.66)
Diabetes	586 (34.3)	1.11 (0.98-1.26)	1.10 (0.97-1.25)	1.03 (0.72-1.47)
Congestive heart failure	534 (31.2)	0.97 (0.85-1.11)	0.80 (0.70-0.93)	0.77 (0.53-1.14)
Stroke	219 (12.8)	1.23 (1.04-1.45)	1.03 (0.86-1.24)	0.95 (0.58-1.59)
Cholesterol level, mmol/L (mg/dL)				
<5.17 (<200)	1091 (63.8)	(Referent)	(Referent)	(Referent)
5.17-6.18 (200-239)	313 (18.3)	1.10 (0.84-1.29)	1.07 (0.91-1.28)	1.54 (1.02-2.32)
$\geq 6.21 (\geq 240)$	306 (17.9)	0.98 (0.83-1.16)	1.12 (0.95-1.31)	1.31 (0.84-2.04)
<b>Medication use on admission</b>				
Aspirin	635 (37.1)		1.84 (1.46-1.88)	3.79 (2.62-5.48)
$\beta$ -Blockers	637 (37.3)	1.85 (1.46-1.88)		2.02 (1.43-2.83)
Lipid-lowering medications	123 (7.2)	1.99 (1.74-2.29)	1.52 (1.27-1.81)	
Calcium channel blockers	751 (43.9)	1.21 (1.07-1.37)	1.10 (0.97-1.25)	1.34 (0.95-1.89)
Diuretics	665 (38.9)	0.88 (0.77-1.00)	0.83 (0.73-0.95)	0.85 (0.59-1.21)
Warfarin	133 (7.8)	0.84 (0.65-1.09)	1.23 (1.01-1.50)	1.28 (0.73-2.28)
Antiarrhythmic medications	166 (9.7)	1.15 (0.95-1.39)	2.01 (1.77-2.27)	1.39 (0.84-2.29)
Digoxin	435 (25.4)	1.00 (0.88-1.15)	0.72 (0.61-0.85)	0.75 (0.49-1.14)

\*Ellipses indicate not applicable.

lesterol level greater than 5.17 mmol/L [ $>200$  mg/dL]. The percentages of patients receiving aspirin,  $\beta$ -blockers, and lipid-lowering medications at hospital admission were 37.1%, 37.3%, and 7.2%, respectively. Concurrent use of additional cardiovascular medications varied, ranging from 43.9% of patients taking a calcium channel blocker to 7.8% of patients taking warfarin.

#### RECEIPT OF ASPIRIN, $\beta$ -BLOCKERS, AND LIPID-LOWERING MEDICATIONS BEFORE ADMISSION FOR RECURRENT AMI

##### Aspirin

The percentages of patients with AMI who were receiving aspirin at hospital admission increased significantly ( $P<.001$ ) during the 6 study years, from 13.5% in 1986 to 52.6% in 1995 (Figure 1). Older patients and women were significantly less likely to be receiving aspirin, whereas patients who had a history of angina or stroke or who were concurrently receiving  $\beta$ -blockers, lipid-lowering medications, or calcium channel blockers were more likely to be receiving aspirin (Table 1).

In the multivariate regression model, 10 demographic and clinical variables were identified as having an independent association with receiving aspirin at hospital admission (Table 2). Enrollment in earlier study years (compared with more recent study years) was associated with

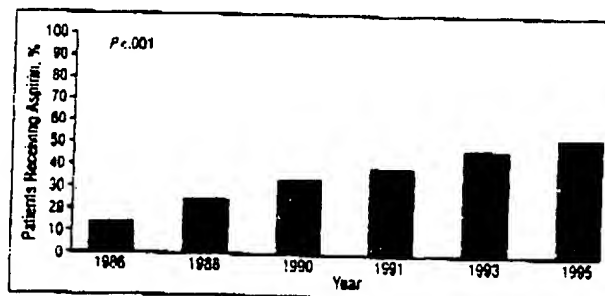


Figure 1. Temporal trends in the receipt of aspirin before hospital admission for recurrent acute myocardial infarction: Worcester Heart Attack Study, 1986-1995.

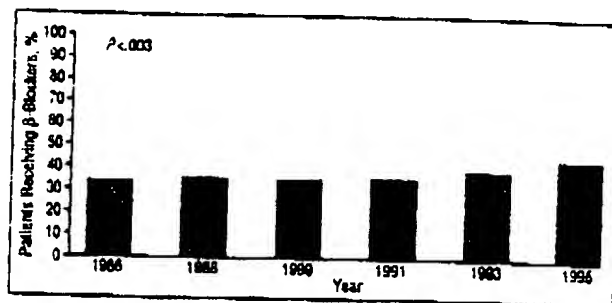
not receiving aspirin (OR, 0.13; 95% CI, 0.09-0.21; comparing 1986 with 1995). Advancing patient age (OR, 0.67; 95% CI, 0.51-0.89; for age  $>75$  years compared with age  $<65$  years) and female sex (OR, 0.78; 95% CI, 0.62-0.98) were also associated with not receiving aspirin. As in the bivariate analysis, history of angina or stroke and concurrent use of several other cardiovascular medications, including  $\beta$ -blockers and lipid-lowering medications, were associated with receiving aspirin.

##### $\beta$ -Blockers

The percentages of patients with AMI who were receiving  $\beta$ -blockers at hospital admission increased mod-

**Table 2. Variables Predicting Receipt of Aspirin Before Admission for Recurrent Acute Myocardial Infarction: Worcester Heart Attack Study**

Variable	Adjusted Odds Ratio (95% Confidence Interval)
Age, y	
<65	1.00 (Referent)
65-74	0.84 (0.64-1.11)
≥75	0.67 (0.51-0.89)
Women	0.78 (0.62-0.98)
Study year	
1986	1.00 (Referent)
1988	0.81 (0.59-1.10)
1991	0.58 (0.41-0.81)
1990	0.44 (0.31-0.63)
1989	0.29 (0.19-0.43)
1988	0.13 (0.09-0.21)
History of angina	1.30 (1.04-1.63)
History of stroke	1.41 (1.02-1.93)
Concurrent β-blocker use	2.14 (1.71-2.67)
Concurrent lipid-lowering drug use	2.61 (1.70-4.00)
Concurrent calcium channel blocker use	1.39 (1.12-1.74)
Concurrent warfarin use	0.45 (0.29-0.68)
Concurrent digoxin use	1.44 (1.12-1.87)



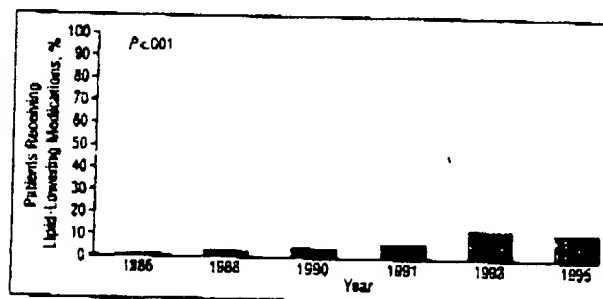
**Figure 2. Temporal trends in the receipt of β-blockers before hospital admission for recurrent acute myocardial infarction: Worcester Heart Attack Study, 1986-1995.**

estly ( $P<.003$ ) during the 6 study years, from 33.2% in 1986 to 44.4% in 1995 (**Figure 2**). Advancing age, white race, a history of congestive heart failure, and use of diuretics or digoxin were associated with not receiving a β-blocker (Table 1). Patients with a history of angina or hypertension or who were concurrently receiving aspirin, lipid-lowering medications, warfarin, or antiarrhythmic medications were more likely to receive a β-blocker.

In the multivariate regression model, 12 demographic and clinical variables were identified as having an independent association with receiving a β-blocker (**Table 3**). Although there was a statistically significant increase in the odds of receiving a β-blocker from 1990 (OR, 0.62; 95% CI, 0.42-0.90) and 1991 (OR, 0.63; 95% CI, 0.43-0.91) to 1995, the odds of receiving this medication in earlier years (1986 or 1988) were no lower than in the most recent study year (1995). As in the bivariate analysis, advancing patient age (OR, 0.75; 95% CI, 0.57-1.00) and white race (OR, 0.53; 95% CI, 0.35-0.72) were associated with not receiving a β-blocker. History of angina or hypertension and concurrent use of other cardiovascular medications, including aspirin and lipid-

**Table 3. Variables Predicting Receipt of β-Blockers Before Admission for Recurrent Acute Myocardial Infarction: Worcester Heart Attack Study**

Variable	Adjusted Odds Ratio (95% Confidence Interval)
Age, y	
<65	1.00 (Referent)
65-74	1.02 (0.78-1.35)
≥75	0.75 (0.57-1.00)
Women	1.05 (0.83-1.32)
White	0.53 (0.35-0.72)
Study year	
1986	1.00 (Referent)
1993	0.75 (0.54-1.05)
1991	0.63 (0.43-0.91)
1990	0.62 (0.42-0.90)
1988	0.83 (0.58-1.24)
1988	0.92 (0.63-1.36)
History of angina	1.73 (1.39-2.14)
History of hypertension	2.19 (1.75-2.76)
Total cholesterol level >5.17 mmol/L (>200 mg/dL)	1.30 (1.03-1.64)
Concurrent aspirin use	2.22 (1.78-2.78)
Concurrent warfarin use	1.72 (1.14-2.60)
Concurrent diuretic use	0.70 (0.55-0.89)
Concurrent antiarrhythmic medication use	5.25 (3.60-7.66)
Concurrent digoxin use	0.57 (0.43-0.76)



**Figure 3. Temporal trends in the receipt of lipid-lowering medications before hospital admission for recurrent acute myocardial infarction: Worcester Heart Attack Study, 1986-1995.**

lowering medications, were again positively associated with receiving a β-blocker.

### Lipid-Lowering Medications

The percentages of patients with AMI who were receiving lipid-lowering medications increased significantly ( $P<.001$ ) during the 6 study years, from 0.8% in 1986 to 11.7% in 1995 (**Figure 3**). Older patients, women, and those not covered by private medical insurance were significantly less likely to be receiving a lipid-lowering medication, whereas patients who had an elevated cholesterol level ( $\geq 5.17$  mmol/L [ $\geq 200$  mg/dL]) or who were concurrently receiving β-blockers or aspirin were more likely to be receiving a lipid-lowering medication (Table 1). This low level of receipt of lipid-lowering medications was despite the finding that more than 36.2% of patients had a total cholesterol level greater than 5.17 mmol/L ( $>200$  mg/dL) (Table 1).

**Table 4. Variables Predicting Receipt of Lipid-Lowering Medications Before Admission for Recurrent Acute Myocardial Infarction: Worcester Heart Attack Study**

Variable	Adjusted Odds Ratio (95% Confidence Interval)
Age, y	
<65	1.00 (Referent)
65-74	0.60 (0.39-0.93)
≥75	0.14 (0.08-0.25)
Women	1.59 (1.04-2.43)
Study year	
1995	1.00 (Referent)
1993	1.11 (0.68-1.80)
1991	0.44 (0.23-0.84)
1990	0.29 (0.14-0.60)
1988	0.16 (0.06-0.44)
1986	0.07 (0.02-0.30)
Total cholesterol level >5.17 mmol/L (>200 mg/dL)	1.77 (1.16-2.69)
Concurrent aspirin use	2.85 (1.88-4.32)
Concurrent calcium channel blocker use	1.53 (1.03-2.27)

In the multivariate regression model, 6 demographic and clinical variables were identified as having an independent association with receiving a lipid-lowering medication (Table 4). Enrollment in earlier study years was associated with not receiving a lipid-lowering medication. Advancing patient age (OR, 0.14; 95% CI, 0.08-0.25) also remained associated with not receiving a lipid-lowering medication. An elevated serum cholesterol level and concurrent use of other cardiovascular medications were, as in the bivariate analysis, also associated with receipt of a lipid-lowering medication. In contrast to the bivariate analysis, women were significantly more likely to be receiving a lipid-lowering medication after controlling for demographic and clinical factors.

#### COMMENT

Evidence-based clinical guidelines strongly endorse the use of aspirin and  $\beta$ -blockers in nearly all patients who have experienced an MI and do not have specific contraindications<sup>14,15</sup> and the use of lipid-lowering medications in those with elevated serum cholesterol levels.<sup>13,16</sup> Studies establishing the efficacy of using these medications for secondary prevention in coronary heart disease, on which these practice guidelines are based, were published before the first year of the present investigation. Despite widespread dissemination of this information, we found that, even by 1995, more than half of all patients who were first seen with recurrent AMI were not receiving aspirin or a  $\beta$ -blocker and that most patients (>90%; two thirds of those with an elevated cholesterol level) were not receiving a lipid-lowering medication. Although receipt of aspirin and lipid-lowering medications increased substantially during the approximately 10-year study, only modest changes were noted for  $\beta$ -blocker use. In addition to comorbidities and concurrent cardiovascular medication use, receipt of these medications was significantly affected by nonclinical factors such as age and sex. These findings suggest substantial

missed opportunities for the prevention of recurrent AMI with the use of these effective therapies.

Results of well-designed clinical trials have been shown to affect the prescription of cardiovascular medications by physicians.<sup>28,29</sup> However, results of several previous studies conducted in the 1990s found significant underuse of aspirin<sup>17,19</sup> and  $\beta$ -blockers<sup>18,20-23</sup> at hospital discharge after an initial AMI despite the demonstrated efficacy of these medications in published clinical trials. Undertreatment of hypercholesterolemia among patients with established coronary heart disease also has been previously described.<sup>34</sup> The low rates of prescribing these medications have been attributed to deficits in physician knowledge of medication effectiveness because of long delays in the dissemination of the results of clinical research to practicing clinicians.<sup>22,34-38</sup> For example, results of a recent study<sup>38</sup> show that the time lag between published meta-analyses that established the efficacy of using aspirin and  $\beta$ -blockers in the secondary prevention of MI and the recommended use of these medications by more than half the authors of review articles and textbook chapters on the subject was 6 and 2 years, respectively. In addition, despite the publication of evidence-based practice guidelines recommending treatment of hypercholesterolemia for patients with established coronary heart disease in 1988,<sup>16</sup> the use of lipid-lowering medications was not yet recommended by more than half the authors of review articles and textbook chapters on the subject 2 years later.<sup>38</sup> This considerable time lag between the publication of results of clinical trials and the acquisition of this knowledge by physicians may be largely responsible for the low percentages of patients receiving aspirin,  $\beta$ -blockers, and lipid-lowering medications that we observed and the dramatic increases in receipt of aspirin and lipid-lowering medications years after their effectiveness was first demonstrated.

We also found that, although aspirin,  $\beta$ -blockers, and lipid-lowering medications were received by relatively small percentages of patients after an MI, these medications were received at even lower levels by several clinically and demographically defined patient subgroups. As expected, patients with cardiovascular risk factors and comorbid conditions tended to be more likely to be receiving any one of the 3 medications of interest, and patients who were currently using any 1 of these medications were more likely to be using another of them. However, nonclinical factors such as age and sex also affected patterns of receipt of these medications. Patients who were older ( $\geq 75$  years) were significantly less likely to use any of the 3 medications, a finding consistent with previous studies that show underuse of  $\beta$ -blockers<sup>20,22</sup> and aspirin<sup>17</sup> in elderly patients at hospital discharge after AMI. Yet, the survival benefit from  $\beta$ -blocker<sup>21,39</sup> and aspirin<sup>1</sup> therapy in patients with established coronary heart disease appears to be at least as great for elderly as nonelderly patients. The benefits of therapy with lipid-lowering medications in elderly patients with established coronary heart disease have not been clearly demonstrated because most large clinical trials do not include adequate numbers of elderly patients. Nonetheless, because there is no evidence that the basic pathophysiological processes underlying coronary atherogenesis

are different for elderly and nonelderly patients. National Cholesterol Education Program guidelines recommend that age alone should not be a reason to treat hypercholesterolemia less aggressively.<sup>13</sup>

Women in the present population-based study were significantly less likely to be receiving aspirin at the time of reinfarction, a finding consistent with that of a previous study<sup>10</sup> showing that aspirin is used less often for women than for men after an initial MI. As with increasing age, results of previous research do not suggest a less beneficial effect of aspirin use in women than in men with previous MI.<sup>1</sup> However, in our multivariate models, being a woman was associated with greater odds of receiving a lipid-lowering agent. Thus, patient sex seems to have a variable effect on the odds of receiving effective therapies at the time of recurrent AMI.

Lack of physician awareness of the results of clinical trials demonstrating the effectiveness of these medications or of practice guidelines recommending the use of these medications irrespective of age or sex may contribute to the low percentages of patients receiving these medications that we observed. It is also likely that use of these 3 medications was affected by the presence of clinical contraindications.  $\beta$ -blocker use is contraindicated in patients with heart block, bradycardia, congestive heart failure, reactive airways disease, diabetes mellitus, and depression, and aspirin use may be contraindicated in patients with bleeding disorders, peptic ulcer disease, thrombocytopenia, and aspirin allergy. Use of lipid-lowering medications is contraindicated in few patients. Because data were only available for a few coexisting illnesses that could constitute a contraindication to medication use, we could not assess the magnitude of the impact of clinical contraindications on the rates of use of these medications. However, of patients screened for possible inclusion in the largest  $\beta$ -blocker trials, the proportion who had contraindications to  $\beta$ -blocker use did not exceed 18%.<sup>7,11</sup> In a previous aspirin trial,<sup>12</sup> the percentage of screened patients who were excluded because of contraindications to aspirin use was less than 4%. Although it is possible that patients with recurrent AMI may have more contraindications to medication use than patients in these clinical trials, it seems unlikely that such differences could completely account for the low medication use rate that we observed.

Beyond physician prescribing practices, the patient's inability to comply with physician recommendations may contribute to lower use rates. It is possible that the cost of long-term therapy may discourage some patients from continuing to use these medications. We found that patients with private insurance were more likely to be using lipid-lowering medications, most classes of which are relatively expensive (eg, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors), at the time of their recurrent MI. This relationship did not persist in the multivariate model, but it is possible that this was caused by either low statistical power because of the small number of patients using lipid-lowering medications or residual confounding by age because patients with nonprivate insurance (including Medicare) were more likely to be older. The relationship between insurance status and use of lipid-lowering medications in patients after an MI, therefore, deserves further study. For use of  $\beta$ -blockers and aspi-

rin, relatively inexpensive medications, we found no association with medical insurance status.

It is also likely that patients' inability to tolerate the adverse effects of these medications contributed to the low usage rates we observed. In a previous large study<sup>14</sup> of patients who have experienced an MI, the Beta-blocker Heart Attack Trial, withdrawal of  $\beta$ -blocker therapy because of adverse effects was 13% for 2 years of follow-up. In the Coronary Drug Project Research Group trial<sup>15</sup> of aspirin for secondary prevention, only 4.5% of patients taking aspirin were compliant with therapy less than 20% of the time during an average of 22 months of follow-up. However, results of a previous study<sup>16</sup> show that rates of discontinuation of lipid-lowering medication use in the primary care setting (primary and secondary prevention patients combined) were variable, depending on the particular agent prescribed, and were higher, in general, than the rates reported in clinical trials. Unfortunately, no data were collected as part of our study that would allow us to assess the impact of this problem on receipt of medications examined in this study.

Although it is likely that each factor discussed has some effect on the rate of use of these medications, physician prescribing behavior is likely to have the greatest impact. Results of previous studies on receipt of aspirin and  $\beta$ -blockers by patients after an MI indicate that physicians do not prescribe these medications to 15% to 25% of eligible patients at hospital discharge. Furthermore, the rapid rise in the use of aspirin and lipid-lowering medications over time in the present study more likely reflects substantial changes in physician prescribing behavior because of the acquisition of new knowledge about health benefits associated with these agents rather than dramatic changes in the prevalence of contraindications to using these medicines or changes in patients' ability to comply with recommended therapy.

Residents of the Worcester metropolitan area are similar to those of the overall United States with respect to characteristics such as age, sex, and socioeconomic status but not for race.<sup>21,20</sup> By including all patients hospitalized with recurrent AMI from a defined geographic area, this study minimized the likelihood of selection biases that may be present in studies of patients hospitalized in single or referral hospitals. Several limitations of this study should also be noted. First, to assess medication use just before admission, we relied on documentation of the patient's outpatient medical regimen in the medical record at hospital admission for recurrent AMI. To the extent that this information in many cases came from patient self-report, inaccuracies in patient recall could have led to some underestimates or overestimates of the rates of use of these medications.

Second, although detailed information about cardiovascular comorbidities and concurrent medication use was available for study patients, information on the complete range of additional comorbidities that could represent absolute or relative contraindications to use of the 3 medications examined was not available. In addition, information about discontinuation of medication use because of adverse effects was not known. Thus, we could not determine the "right" percentage of patients who should have been receiving each medication we examined. Third, although this study highlights the small percentages of patients receiving these medications in ac-



nal practice, we were not able to assess the reasons underlying these patterns of care. Future studies will need to address the relative impact of physicians' failure to prescribe these medications and patients' inability or choice not to comply with recommended therapies.

In summary, this study documents the extent of underuse of aspirin,  $\beta$ -blockers, and lipid-lowering medications by patients with a previous history of MI who later experience a recurrent AMI and identifies clinical and non-clinical factors associated with this underuse. Although the rates of use of the cardiovascular medications we studied may be higher for patients after an MI who did not have a recurrent event (to the extent that these medications are effective), our findings confirm that there remain substantial missed opportunities to treat patients after an MI with medications that are shown to reduce the risk of recurrent MI and cardiovascular death. Given the high prevalence of MI, concerted efforts should be undertaken to facilitate more rapid transmission of the results of clinical trials of cardiovascular medications to practicing physicians and to reduce substantial variation in treatment practices that seems to be related to patient age and sex.

Accepted for publication July 14, 1998.

Supported by grant HL R01 54534 from the National Institutes of Health, Bethesda, Md.

This research was made possible by the cooperation of the medical records, administration, and cardiology departments of participating metropolitan Worcester, Mass, hospitals.

Reprints: Danny McCormick, MD, MPH, Division of General Medicine, University of Massachusetts Medical Center, 55 Lake Ave N, Worcester, MA 01655.

## REFERENCES

1. Collaborative overview of randomized controlled trials of anti-platelet therapy in various categories of patients. *BMJ*. 1994;308:81-106.
2. Becker RC. Antiplatelet therapy in coronary heart disease. *Arch Pathol Lab Med*. 1993;117:89-98.
3. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I: treatments following myocardial infarction. *JAMA*. 1988;260:2086-2093.
4. Pederson TR. Six-year follow-up of the Norwegian multicenter study on timolol after acute myocardial infarction. *N Engl J Med*. 1985;313:1055-1058.
5. Hjalmarsson A, Elmfeldt D, Harlitz J, et al. Effect on mortality of metoprolol in myocardial infarction: a double-blind randomized trial. *Lancet*. 1981;2:823-827.
6. Beta-blocker Heart Attack Study Group. The Beta-blocker Heart Attack Trial. *JAMA*. 1981;246:2073-2074.
7. The Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med*. 1981;304:801-807.
8. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction. *Prog Cardiovasc Dis*. 1985;27:335-371.
9. The Beta-blocker Pooling Project Research Group. The Beta-blocker Pooling Project (BBPP). *Eur Heart J*. 1988;9:8-16.
10. Holm I. An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. *Circulation*. 1990;82:1916-1924.
11. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
12. Sachs FM, Pfeiffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001-1009.
13. National Cholesterol Education Program Expert Panel. Second Report on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation*. 1994;89:1333-1445.
14. Gunnar RM, Boardman PVD, Dixon JW, et al. ACC/AHA guidelines for the early management of patients with acute myocardial infarction. *J Am Coll Cardiol*. 1990;16:249-292.
15. ACC/AHA Task Force. Guidelines for the management of patients with acute myocardial infarction. *J Am Coll Cardiol*. 1996;28:1328-1428.
16. National Cholesterol Education Program Expert Panel. Report on detection, evaluation and treatment of high blood cholesterol in adults. *Arch Intern Med*. 1988;148:36-69.
17. Malone ML, Sial SH, Battista RJ, Nachodsky JP, Solomon DJ, Goodwin JS. Age-related differences in the utilization of therapies post acute myocardial infarction. *J Am Geriatr Soc*. 1995;43:627-633.
18. Ellerbeck EF, Jenks SF, Radford MJ, et al. Quality of care for Medicare patients with acute myocardial infarction. *JAMA*. 1995;273:1509-1514.
19. Krumholz HM, Radford MJ, Ellerbeck EF, et al. Aspirin for secondary prevention after acute myocardial infarction in the elderly: prescribed use and outcomes. *Ann Intern Med*. 1996;124:292-298.
20. Sial SH, Malone M, Freeman JL, Battista R, Nachodsky J, Goodwin JS. Beta blocker use in the treatment of community hospital patients discharged after myocardial infarction. *J Gen Intern Med*. 1994;9:599-605.
21. Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L. Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. *JAMA*. 1997;277:115-121.
22. Viskin S, Kizile I, Lav E, et al. Treatment with  $\beta$ -adrenergic blocking agents after myocardial infarction. *J Am Coll Cardiol*. 1995;25:1327-1332.
23. Brand DA, Newcomer LN, Freiburger A, Tian H. Cardiologists' practices compared with practice guidelines: use of beta-blockers after acute myocardial infarction. *J Am Coll Cardiol*. 1995;26:1432-1436.
24. Goldberg RJ, Gore JM, Alpert JS, et al. Cardiogenic shock after acute myocardial infarction: incidence and mortality from a community-wide perspective, 1975 to 1988. *N Engl J Med*. 1991;325:1117-1122.
25. Goldberg RJ, Gore JM, Alpert JS, Dalen JE. Non-Q wave myocardial infarction: recent changes in occurrence and prognosis: a community-wide perspective. *Am Heart J*. 1987;113:273-279.
26. Goldberg RJ, Gore JM, Gurwitz JH, et al. Impact of age on the incidence and prognosis of initial acute myocardial infarction: the Worcester Heart Attack Study. *Am Heart J*. 1989;117:543-549.
27. Gurwitz JH, Goldberg RJ, Chen Z, Gore JM, Alpert JS. Recent trends in hospital mortality of acute myocardial infarction: have improvements been realized for all age groups? the Worcester Heart Attack Study (1975-1990). *Arch Intern Med*. 1994;154:2202-2208.
28. Col NF, McLaughlin TJ, Soumerai SB, et al. The impact of clinical trials on the use of medications for acute myocardial infarction: results of a community-based study. *Arch Intern Med*. 1996;156:54-60.
29. World Health Organization. *International Classification of Diseases, Ninth Revision (ICD-9)*. Geneva, Switzerland: World Health Organization, 1977.
30. Goldberg RJ, Gore JM, Alpert JS, Dalen JE. Recent changes in attack and survival rates of acute myocardial infarction (1975-1981): Worcester Heart Attack Study. *JAMA*. 1988;255:2774-2779.
31. Goldberg RJ, Gore JM, Alpert JS, Dalen JE. Incidence and case fatality rates of acute myocardial infarction (1975-1984): Worcester Heart Attack Study. *Am Heart J*. 1988;115:761-767.
32. Goldberg RJ, Gorak EJ, Yarbowski J, et al. A community-wide perspective of gender differences and temporal trends in the incidence and survival rates following acute myocardial infarction and out-of-hospital deaths due to coronary heart disease. *Circulation*. 1993;87:1947-1953.
33. Lamas GA, Pfeiffer MA, Harro P, Wertheimer J, Rouleau J-L, Braunwald E. Do the results of randomized clinical trials of cardiovascular drugs influence medical practice? *N Engl J Med*. 1992;327:241-247.
34. Cohen MV, Byrne M, Levine B, Gutowski T, Adelson R. Low rate of treatment of hypercholesterolemia by cardiologists in patients with suspected and proven coronary artery disease. *Circulation*. 1991;83:1284-1304.
35. Paasos CL, Newhouse JP, McNeil BJ. Temporal changes in the care and outcomes of elderly patients with acute myocardial infarction, 1987 through 1990. *JAMA*. 1993;270:1832-1836.
36. Phillips BG, Yim JM, Brown EJ, et al. Pharmacologic profile of survivors of acute myocardial infarction at United States academic hospitals. *Am Heart J*. 1996;131:872-878.
37. Montague TJ, Ikuta RM, Wong RY, Bay KS, Teo KK, Davies NJ. Comparison of risk and patterns of practice in patients older and younger than 70 years with acute myocardial infarction in a two-year period (1987-1989). *Am J Cardiol*. 1991;68:843-847.
38. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. *JAMA*. 1992;268:240-248.
39. Jansen RWM, Gurwitz JH. Controversies surrounding the use of beta blockers in older patients with cardiovascular disease. *Drugs Aging*. 1994;4:175-183.
40. Schwartz LM, Fisher ES, Tosteson ANA, et al. Treatment and health outcomes of women and men in a cohort with coronary artery disease. *Arch Intern Med*. 1997;157:1545-1551.
41. Beta-blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I: mortality results. *JAMA*. 1982;247:1707-1714.
42. Sanz G, Pajaron A, Alegria E, et al. Prevention of early aortocoronary bypass occlusion by low-dose aspirin and dipyridamol. *Circulation*. 1990;82:765-773.
43. The Coronary Drug Project Research Group. Aspirin in coronary heart disease. *J Chronic Dis*. 1976;29:625-642.
44. Andrade SE, Walker AM, Gottlieb LK, et al. Discontinuation of antihypertensive drugs: do rates reported in clinical trials reflect rates in primary care settings? *N Engl J Med*. 1995;332:1125-1131.

# HEDIS 2000 Narrative

*What's in  
It and Why  
It Matters*

*AG & P. Org  
Hedis Measures Development*

NC A

#### 42 Effectiveness of Care

the visit, and then mailed back with results. Other MCOs send reminder "birthday" cards encouraging women to receive recommended Pap tests. Allowing an annual OB/GYN visit without a referral also removes one potential barrier to cervical cancer screening, and may help boost screening rates.

##### ***Prenatal Care in the First Trimester***

This measure looks at how well our delivery system works for newly pregnant women. It estimates the percentage of pregnant women in the MCO who began prenatal care during the first 13 weeks of pregnancy. Care can be delivered by a variety of appropriate obstetrical, primary care or nurse midwifery providers.

The concept of prenatal care is a prototype of preventive medicine. Healthy diet counseling, vitamin supplementation, identification of maternal risk factors and health promotion all need to occur early in pregnancy to have a maximum impact on outcomes. Poor outcomes include spontaneous abortions, low birthweight babies, large for gestational age babies, neonatal infections and countless others.

Early prenatal care is also an essential part of what is needed to help a pregnant woman prepare to become a mother.

---

Nationally, 10 percent of MCOs had rates for prenatal care in first trimester of 95.1 percent or greater, as of 1998. If the rest of MCOs performed at this level, preventable loss of life and illness could be avoided.

---

*What can MCOs do to improve rates of prenatal care in first trimester?* MCOs and providers should develop comprehensive exercise and educational programs for pregnant women focusing on the importance and benefits of prenatal care for both mothers and infants and about the significant risks associated with drug or alcohol use during pregnancy. MCOs should also consider developing incentive programs to encourage broader participation in such programs. Assigning case managers to high-risk members may also help encourage appropriate prenatal care and decrease dangerous behaviors.

##### ***Check-Ups After Delivery***

This measure looks at the care rendered to women after they have delivered a baby. It estimates the percentage of women who had live births who had a postpartum visit between 21 days and 56 days after delivery.

The eight weeks after giving birth are a period of physical, emotional and social changes for the mother, during a time when she is also adjusting to caring for her new baby.

In order to give clinicians that care for new mothers the chance to offer advice and assistance, the American College of Obstetricians and Gynecologists recommends that women see their health care provider at least once between 4 and 6 weeks after giving birth. The first postpartum visit should include a physical examination, and an opportunity for the health care provider to answer parents' questions and give family planning guidance and counseling on nutrition.

##### ***Beta Blocker Treatment After a Heart Attack***

This measure looks at one way of preventing a second heart attack. It estimates the number of MCO members who were discharged from the hospital, after surviving a heart attack, who received a prescription for a type of drug called a beta blocker. Excluded are those who have a valid medical reason not to take the drug.

Heart disease is the leading cause of death in the U. S., and every year more than 500,000 Americans die from it. The American Heart Association estimates that the total annual cost of medical care and lost productivity due to heart disease is \$12 billion to \$24 billion. Annually, approximately 1.5 million Americans suffer a heart attack.



A heart attack occurs when the blood supply to part of the heart muscle is severely reduced or stopped and heart tissue is destroyed by a lack of oxygen.

People who have had a heart attack are at high risk of having another one. One medical therapy that has been shown to lower that risk is the use of beta blockers, which lower blood pressure and reduce how hard the heart has to work.

Nationally, 10 percent of MCOs had rates for beta blocker treatment after a heart attack of 93.1 percent or greater, as of 1998. If the rest of the MCOs performed at this level, more than 2,000 cardiac deaths would be avoided each year. The number of future heart attacks avoided would be even higher. Expenditures for cardiac care would also be reduced by tens of millions of dollars annually.

*What can MCOs do to improve beta blocker treatment rates?* Many physicians are unaware of the extent to which these drugs improve cardiac outcomes, and therefore fail to prescribe them when appropriate. The key to improving rates of use is for the MCO to educate providers about the value of these agents, provide incentives to encourage their use, and provide physicians with guidelines and other decision support tools that will assist them in prescribing drugs appropriately.

### ***Cholesterol Management After Acute Cardiovascular Events***

Each year, about 1.5 million people are diagnosed with coronary artery disease and almost half a million die from the disease. Coronary heart disease remains the single leading cause of death in America today.

This measure assesses two components of cholesterol management for persons who are known to have heart disease by virtue of having had an acute cardiovascular event within the prior year: the percentage of members who have an LDL-C screening and the percentage of members who have a documented LDL-C level below 130 mg/dL.

Total blood cholesterol is directly related to the development of coronary artery disease and coronary heart disease, with most of the risk associated with LDL cholesterol. When LDL-C levels are high, cholesterol can build up within the walls of the arteries causing atherosclerosis, the build-up of plaque. Hemorrhaging or clot formation can occur at the site of plaque build-ups, blocking arteries and causing heart attack and stroke.

Reducing cholesterol in patients with known heart disease is critically important, as treatment can reduce morbidity (heart attacks and strokes) and mortality by as much as 40 percent. The National Cholesterol Education Program, NCEP, has laid out guidelines for the management of cholesterol in patients with heart disease. These guidelines establish the need for close monitoring of LDL-cholesterol in patients with coronary heart disease, and set a target for low density lipoprotein cholesterol (LDL-C) of 100 mg/dL or less for such patients.\*

NCQA supports the NCEP recommendation that the target for therapy in patients with coronary heart disease is an LDL-C less than or equal to 100 mg/dL. The HEDIS measure nonetheless sets the target at an LDL-C less than 130 mg/dL for two important reasons. First, several appropriate therapeutic options exist for further risk reduction in patients with LDL-C between 100 mg/dL and 130 mg/dL; not all of which are likely to bring LDL-C to below 100 mg/dL. Clinicians should not be penalized for selecting these options when they feel that they are most appropriate for their patients. Second, few patients with coronary heart disease are currently reaching NCEP goals; the measure as we have defined it is more likely to permit those MCOs that are successfully making progress toward these goals to be recognized

\* The NCEP guidelines—as well as other materials that may help managed care organizations improve the management of patients with high cholesterol—can be obtained from the National Heart, Lung, and Blood Institute Health Information Network: PO Box 30105, Bethesda, MD 20824-0105. Phone: 301-592-8573; Fax: 301-592-8563; E-mail: nhlbiinfo@rover.nhlbi.nih.gov.

Exhibit 8

1: J Am Geriatr Soc 1998 May;46(5):615-6

Comment in:

J Am Geriatr Soc. 1999 Jan;47(1):120-1.

Underutilization of aspirin in older patients with prior myocardial infarction at the time of admission to a nursing home.

Aronow WS.

Hebrew Hospital Home, Bronx, New York 10475, USA.

OBJECTIVE: To investigate the prevalence of aspirin use in older patients with prior myocardial infarction at the time of admission to a nursing home. DESIGN: In a prospective study, the prevalence of aspirin use in 350 consecutive older patients with documented Q-wave myocardial infarction and no contraindications to aspirin use was investigated in patients aged 60 years or older at the time of admission to a nursing home. SETTING: A large, long-term, healthcare facility. PATIENTS: The patients included 231 women and 119 men, mean age 81 +/- 8 years (range 60 to 100). MEASUREMENTS AND MAIN RESULTS: Of the 350 patients with documented Q-wave myocardial infarction and no contraindications to aspirin therapy, 60 patients (17%) were receiving aspirin at the time of admission to the nursing home. CONCLUSION: There is a marked underutilization of aspirin in the treatment of older patients with documented prior myocardial infarction at the time of admission to a nursing home.

PMID: 9588376 [PubMed - indexed for MEDLINE]

Exhibit 5

1: Can J Cardiol 1999 Mar;15(3):291-6

Underuse of acetylsalicylic acid in individuals with myocardial infarction, ischemic heart disease or stroke: data from the 1995 population-based Nova Scotia Health Survey.

Rojas-Fernandez CH, Kephart GC, Sketris IS, Kass K.

Texas Tech University Health Sciences Center, School of Pharmacy, Amarillo, TX, USA. carlosr@cortex.ama.ttuhscc.edu

**OBJECTIVE:** To determine current patterns of acetylsalicylic acid (ASA) use in Nova Scotia for individuals with self-reported myocardial infarction, stroke or ischemic heart disease. **DESIGN:** Descriptive, cross-sectional, population-based study using data from the 1995 Nova Scotia Health Survey (NSHS). The NSHS was based on a probability sample and was representative of the Nova Scotia adult population by age, sex and region. Survey data were obtained by standardized home interviews conducted by trained public health nurses. **SETTING:** The province of Nova Scotia in 1995. **PARTICIPANTS:** Survey respondents who reported having a myocardial infarction, stroke or ischemic heart disease were assessed. **RESULTS:** Among those who reported a history of myocardial infarction, stroke or ischemic heart disease, 55% (95% CI 47% to 63%), 49% (95% CI 38% to 61%) and 54% (95% CI 39% to 68%), respectively, reported using ASA at the time of the survey. Overall, only 53% of those with cardiovascular disease were using ASA. Exclusion of persons with potential contraindications to ASA did not significantly increase these proportions. **CONCLUSIONS:** ASA appears to be underused in those at high risk for future vascular events. Further research is required to investigate determinants of ASA use and to increase appropriate use of ASA.

PMID: 10202192 [PubMed - indexed for MEDLINE]